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Remarks on the Scope and Organization

OF THE

PATHOLOGICAL INSTITUTE

OF THE

NEW YORK STATE HOSPITALS.

BY

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REMARKS ON THE SCOPE AND ORGANIZATION OF THE PATHOLOGICAL INSTITUTE OF THE NEW YORK STATE HOSPITALS.*

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Gentlemen:

Surely there is no chapter in the history of all medical science more replete with the record of difficult and intricate research than that which relates to the development of our knowledge of the nervous system, the noblest and most marvelously organized tissue of the body. And yet, notwithstanding the supremacy of the nervous system over all of the other organs and tissues of the body, in its wonderfully intricate organization, nowhere else in the body can we localize and establish the nature of the lesions with such fascinating accuracy as in the neural diseases. And this great mass of knowledge whereby the physical basis of the symptoms in neural diseases can be premised so accurately has been sought out by the clinician. In no department of medical science has the observation of the keen, alert practitioner been of such inestimable service to the anatomist and physiologist as in the nervous system.

However important animal experimentation and laboratory work may have been in the elucidation of questions in structure and function in the nervous system it has ever been the experiments which nature has evoked in man, in the diseases of the nervous system, that have been crucial and brilliantly decisive in the development of neuro-path-

* By invitation, Dr. Van Gieson was invited to meet in regular monthly conference, the Medical and General Superintendents of the State Hospitals and the State Commission in Lunacy and to outline the probable future work of the Institute, and its relation to the several hospitals. The Editorial Committee consider his address of value to those members of the medical staffs who were not present at the conference, and by Dr. Van Gieson's permission his address is herewith published, with the understanding that it shall be received as informal as was its presentation. Ed. Com.

ology, of the localization of function, architecture of the fibre systems, and many other phases of neurology. It has been the practitioner of medicine in the rush of his humane and trying duties who has again and again found such opportunities to play the rôle of the scientific pathologist as has led to the utilization of rare and decisive cases of human brain and cord lesions for the building up of our knowledge of these supreme organs so baffling to research in their intricate structure.

It would be most interesting, had we time, to review the slow, patient development of our conceptions of the structure and function of the nervous system, and trace the studies at the bedside, in the asylum, hospital and dispensary, and in the laboratory, which have contributed each in their measure, each indispensable, to the building up of this knowledge of the structure of the human nervous system and of the nature of its diseases.

It seems to be a tendency of the mind to dwell on results rather than to enquire how they were brought about. And the younger generation of pure scientists, in medicine especially, in these days of the revolutionizing achievements of the pathological and bacteriological laboratories, do not fully realize that it is to the clinician that we owe the great bulk of our knowledge of disease processes and much of physiological science. And this is especially true in regard to our insight into the structure, functions, and pathology of the nervous system. The pathologist described changes, but it remained for the clinician to interpret them; and where clinical data and pathological findings seemed at variance the clinician has given the crucial decision.

The clinicians like Türck, Duchenne, Westphal, Leyden, Erb, Broca, Charcot and Gudden have built up the knowledge of the diseases of the nervous system and have contributed much indeed to our understanding of its functions and their localization, as well as the pathways of the fibre systems. Clinicians like these explained the significance of the findings of the autopsy table; they guided the

work of the pathologist who followed the footsteps of these pioneers in the pathways of the knowledge of the human nervous system and its diseases.

At the present time, however, work along the older lines of research in the pathology of the nervous system is well-nigh exhausted. The limitations of the previous methods of investigation, whereby so much has been accomplished by the clinician and the pathologist in explaining so well causes and morbid processes underlying many nervous diseases, have been growing painfully evident in the past few years. The great method of Golgi, the advances in minute anatomy of the cell, has given the laboratory an unexpected power and prominence in penetrating far beyond the barriers of the previous decade in elucidating neuro-pathological problems.

The whole scope of neuro-pathological laboratory work is upon an entirely different plane than ten years ago; it has an hundredfold more scrutinizing channels of investigation and rests upon a broader and more philosophical basis. Ten years ago nothing could be expected to be attained in seeking for the physical basis of mental diseases. The methods were too coarse; they revealed absolutely nothing of the wonderful microcosm in the internal organization of the ganglion cell and consequently the most minute and delicate but none the less definite and significant changes in the ganglion cells were completely ignored; and it is to some of these new conceptions of investigating neuro-pathological problems, born of new methods and precise knowledge of the normal anatomy of the nervous system, that I would invite your attention. A consideration however of the fields of application of the recently inaugurated Pathological Institute of the State Hospitals of New York involves such a broad and philosophical presentment of the whole scope of modern neurology, as well as the course of its progress for the next two or three decades, that in addressing you upon this almost limitless subject, I may well ask for the freedom of an informal speaker, rather than the attitude

of the elaborate writer. A review of the scope of the Institute would embody not only a discussion of the biology of the nervous system but also of the pathology of mental and nervous diseases, both in regard to what has been accomplished in the investigation of their causes, as well as what remains to be attained along the lines of the comparatively recently discovered and powerful methods of research. We may, then, merely sketch in outline, rather than attempt to present a complete view of the prospective lines of work of the Institute.

It is certainly fundamentally important to point out at the very beginning that no investigations of the highest order of scientific value, of the permanent and philosophical order, can be brought out of the Institute without a development that grows from a comprehensive basis. The only way to advance the knowledge of mental pathology is to study this department of neurology hand in hand with all of the other branches of neurology and to be ever mindful that it is governed by the same laws as morbid processes elsewhere in the body. Mental pathology is, therefore, to be studied in the light of general pathological anatomy.

The Institute should have a staff of scientists each of whom should be especially trained in one or the other of the specialized departments of modern neurology, for it is only by the correlation of all of these departments that the proper and valuable kind of investigation toward the solution of the causes of nervous and mental diseases can be attained. And while, of course, the chief aim of the Institute is to study the physical basis of insanity, this is to be carried out by a knowledge of the nervous system from all its standpoints, and of the general laws of pathology. If the work of the Institute, however, be restricted to the field of mental pathology and lacks the broader conception of its problems conferred by the knowledge of the other departments of neurology, the results will be comparatively useless to science for they can not be intelligently interpreted.

The pathological problems of insanity must be studied

hand in hand with general pathology, general pathology of the nervous system exclusive of the insanities, experimental pathology, physiological chemistry and normal neural anatomy, comparative anatomy and biology of the nervous system, the physiology, cytology, and cytological chemistry of the nerve cell, and bacteriology especially in its relation to the production of toxæmias of the nervous system. To this must also be added a most valuable factor of experimental pathology, namely, the effects on the nervous system of toxæmias and intoxications produced experimentally in animals. Now the intimate association of all of these departments of science is so imperative for the elucidation of the complex problems of neuropathology, that we cannot hope to make any real or lasting headway in explaining the physical basis of insanity without a reciprocal relation between them in the practical work of the laboratory.

Specialization is a valuable factor in scientific research, but its value is practically shown only in its fraction of the whole subject of pathology of which its specialty is but a ramifying branch. While specialization, therefore, is valuable for details, for the discovery of new facts and methods and extending the knowledge of any one of the head sciences, if pursued without reciprocity of associate branches, it cannot always be trusted to properly interpret these facts or obtain the ultimate goal desired of establishing causes and their laws. Hence, the Institute must not be expected, to focus its energies upon the study of mental pathology to the exclusion of other branches of neurology. It must study mental pathology, with the broad conception to be gained by investigation from the correlation of all of the subbranches of neurology. There should be a division of all the special departments of neurology, among the permanent staff of the Institute, and the staff should be thus selected with a view of diversifying the character of its studies. Among the contemplated number of five associates in the Institute, one should have a special training in hæmatology, another in biology and embryology of the nervous system, another in physiological chemistry, still another should

have a special training to conduct and plan out work in toxæmias and intoxications of the nervous system with a special reference to the induction of these conditions experimentally in animals, and finally another associate should be a trained bacteriologist.

It is obvious then, that to conduct the investigations of the Institute along such diversified and specialized lines as these, its staff should not be entirely removed from the influences of the great centres of medical learning, namely, the laboratories, chemical, physiological and pathological of the medical colleges. It is here that the advanced methods, ideas and work invariably come out first. These institutions govern the scientific world, they make the discoveries and are foremost in the ranks of advancing science. The Institute, therefore, by maintaining relations with such institutions, receives the advantages of all the other departments of pathology necessary for this specialized department, without maintaining its equivalent in the Institute proper. If the State laboratory, therefore, is to reap the greatest possible advantages its officers should be in sufficient touch with one or more of the centres of medical learning to absorb the benefits of their diversified specialties, and apply such knowledge as an ally to the specialized work of the Institute in its broadest application.

While the State laboratory will have certain advantages in its systematic organization over the medical collegiate laboratories, it can never provide for the enormous diversity and specialization of study in force at the university centres of medical learning. This the State laboratory can never hope to attain; it can not become a university; it can not maintain a perfectly equipped physiological laboratory, for instance, with all of its apparatus as well as four or five men prominently identified with physiology, who are devoting their life-work to the elucidation of physiological problems and the teaching of this branch. Neither can it maintain laboratories of the same kind in physiological chemistry, bacteriology, general pathology, and photography.

The Institute, it is hoped, therefore, may avail itself of the benefits of the perfectly equipped departments which are in force at the medical colleges. It would seem wholly unnecessary to duplicate work the results of which can be so readily obtained by a neighborhood of laboratories.

It is entirely appropriate to emphasize the importance of the collegiate associations of the Pathological Institute, for it is a matter of fundamental value to conduct neurological investigations on a broad basis and to prevent the Institute from drifting into one specialized field of investigation at the expense of other departments of modern neurology. The fact has always asserted itself, and still does, that the real progress of science has been made in the university centres of learning, or in such institutes as have been more or less closely associated with the university, and medical laboratories isolated or excluded from university influences have invariably failed to make any signal mark on the pages of science.

The inauguration of the Pathological Institute of the State Hospitals occurs at a most felicitous period in the science of neurology for the prosecution of its work. The marvelous precision which the anatomy of the nervous system has reached within the last ten years has really been a renaissance period in the history of neurology. The present day marks an epoch in the history of the evolution of the nervous system. Our knowledge of its construction, the development and ramifications of the central nerve fibre and their connections is definite and accurate and free from the controversial obscurity of the past fifty years. It would be interesting to glance over the history of neurology for the past fifty years and pass over the great landmarks which have made our conceptions of the nervous system so precise and logical, both in its anatomy and physiology. It will be sufficient, at the present time however, to merely emphasize the precise basis of the anatomy and physiology of the nervous system, for when once the anatomy and physiology of an organ or tissue is clear or unequivocal, we are then in a position to build up knowledge

of its abnormal conditions which is lasting and useful. Thus the day is at hand to begin anew the study of the abnormal conditions of the nervous system on a clear and permanent basis, and in the next two decades, or perhaps in less time, with the rapid increase in the ranks of investigators, we shall see an epoch in neuro-pathology fully as striking as is the present one in the normal anatomy and physiology of the nervous system.

The methods of Weigert, Golgi and Nissl, together with the researches of His, Golgi, Retzius, Kölliker, Lenhossek, Cayal and their colleagues have been the prominent factors in revolutionizing our knowledge of neurology, and have opened the way for the new era in neuro-pathology. The older data in this field must be revised and the new data are now capable of intelligent interpretation. Of all of the new discoveries in method, however, which have been the real factors in gaining this new knowledge of the nervous system, Nissl's method is destined to be of untold importance, in solving new problems in neuro-pathology and interpreting the older ones. The importance of Nissl's procedure is not so much due to its innovation as a method, but that it premises exact fixation of the nerve cells, and the application of staining methods to satisfy the searching glance of modern cytology into the delicate and extremely complicated protoplasmatic and nuclear organization of the nerve cell.

Within the past ten or fifteen years the knowledge of minute cell anatomy has made vast strides, so that it is well dignified to the status of a separate science, namely, that of cytology or cellular biology.

Singularly enough, during all this time of the accumulation of marvelously searching results in the knowledge of cell anatomy, the general pathologist neglected to apply this accumulated knowledge to the solution of his own problem. He was rather more concerned with the gross and topographical distribution of lesions and the grouping of diseased cells than with the changes in the cells themselves. It is precisely, however, to these tiny units of the organs

of the body that attention must be directed in studying many of the great groups of disease which are still at the present day obscure, and due to the presence in the body of some form of poison whether it be due to the product of bacteria or to the presence of excretions or secretions produced by some of the organs of the body, or an abnormal condition of the blood, or even to a poison from an extrinsic course. Many of these poisons may at times leave coarser or grosser lesions in the body, which may be recognized by the older and less searching methods of the pathologists, which leave entirely out of view the scrutiny of very minute and delicate changes in the anatomy of the cells as individuals. Yet, in very many cases these subtle poisons frequently leave but little trace of their action, except in the organization of the individual cells of the organs or tissues of the body. The cells are not destroyed or changed in large groups or clusters and if viewed by methods which are not especially adapted to the cell itself, there appears to be no striking change in either the protoplásm or nucleus. If however, we take a case of death from many of these poisons, which seem to leave no visible trace of their action, fix and stain the cells with all of the delicate and complicated technique of the modern cellular biologist, we shall be able to bring out hidden changes of the most minute and delicate character in the parenchyma cells of the viscera. The nervous system is especially sensitive from the complex organization of the ganglion cell to the action of these several poisons, which are the cause of so many manifestations of disease, and the ganglion cells show most exquisitely the traces of many of them whether they be of extrinsic character or in the nature of toxæmias or intoxications.

While it has probably always been suspected that by far the larger majority of diseases has been due to the circulation in the body of intrinsic poisons, yet the evidence assuring this belief has been the gradual accumulation of very recent years. Long before pathology had begun to make any

advances the continued fevers, the exanthemata, syphilis, tuberculosis, rabies, tetanus, hydrophobia, in fact all the infectious and contagious diseases were naturally thought to be the manifestations of poisons which either gained access to the body or which were elaborated within the body. When the study of pathology made advances, evidences of these diseases being due to a poison were found in the occurrence of more or less extensive necroses of the tissues or organs. When bacteriology gained ground, definite micro-organisms were shown to have a causal relationship to several of these diseases, which could be induced experimentally in animals, and furthermore when it was proved that certain poisons attending the development of these organisms were absorbed by the body and were responsible for many of the symptoms, the evidence was complete and final for many individual examples of these diseases. Then a definite explanation was given for the occurrence of necroses of the tissues or organs, or the degenerations or cell proliferations which had been observed in the study of the lesions attending these diseases. Diphtheria is a most brilliant example of the perfection of our understanding of how the toxine or toxalbumen, as these poisons are termed, associated with the growth of bacteria, acts in producing the symptoms of the disease.

It now remains for pathologists to trace out much more accurately than they have hitherto attempted the actions of these toxines, upon the delicate organization of the cells as *individuals*. Some general laws must be established of the action of these toxines, not upon masses of cells in the later stages of their action, but of the initial action of the toxine upon all of the detailed structures of the protoplasm and nucleus. As studies of this kind accumulate, from the standpoint of the cytologist, we shall find traces of the actions of poisons in many of the obscure diseases of the present day which seem to leave no clue of their action, and have until recently been regarded by both the clinician and the pathologist as diseases *sine materia*. Thus, at the present day, inasmuch as the cell knowledge accumulated

by the cellular biologist within the past twenty years is being applied by the pathologist to his problems, it may be well to speak of pathological cytology in contradistinction to normal cytology, and Virchow's term "cellular pathology" used so many years ago will commence at the present time to take on a deeper meaning. By normal cytology we mean a description of all of the minutiæ of the cells of the human body, followed out to an extent indicated by the specialized terminology of the modern cytologist; and by pathological cytology as applied to the human body, any and all of the changes which may affect any of these minute details of cell organization under the influence of disease or abnormal conditions.

If the cytologist has pursued his studies of the cell to such a marvelous depth as to premise a physical basis for heredity in the chromatin of the cell, the pathologist of the present day certainly has an encouraging stimulus to search out clues for the causes of the unexplained diseases. An example always makes a general statement forcible, and the history of the pathology of hydrophobia is so interesting in showing the treasures of knowledge unearthed by the application of cytological studies, that it is well worth glancing at. Until two years ago practically nothing had been found to explain the symptoms of this disease. Yet here was a disease which gave the most dramatic evidence of the extreme irritation, and even destruction, of the elements of the central nervous system. Yet, when examined by the coarser methods of general topographical pathology, practically nothing was found to give any real explanation of the symptoms. At times hemorrhages and leucocytosis about the vessels of the spinal cord and medulla were found, but the ganglion cells were found in place, properly arranged, and the impression was that here was a poison which, although it acted most violently on the ganglion cells, left no changes in them; and this is probably the impression given by most of the text-books on pathology up to within a very recent period. Now, if the nervous system from a case of hydrophobia is studied from a stand-

point of pathological cytology, a brilliant chapter can be written, which gives step by step the impress of a subtle, invisible poison on the ganglion cells, and explains with most interesting clearness just why and how the symptoms arise.

In applying the methods and knowledge of advanced cell studies to the study of hydrophobia, a perfectly definite series of changes can be observed in both the nucleus and cell body, which are almost entirely hidden from view in the coarser and older technical methods of pathology which were subservient to a topographical view of the constituents of an organ or tissue, rather than an elaborate view of the cellular microcosms composing them. By these methods the insight into the ganglion cell organization is so scrutinizing that within six hours after the onset of the symptoms when the rabid animal exhibits nothing more than fine general tremors, changes can be found in the cerebellar ganglion cells. Golgi, also, in applying his own method to the study of hydrophobia, although it certainly has not the advantages, in many respects of the application of aniline dyes to sublimate hardened material, found initial dissolution of the ganglion cell nucleus, occurring at a very early period of the disease, and simultaneously with karyokineses of the endothelial cells of the capillaries in the nervous system. Thus, we can see how cytological investigation has cleared up the manifestations of hydrophobia, and given us very positive evidence of the progressive destruction of the ganglion cells from the action of a poison. Just where this poison comes from, or to what extent a disorganized condition of the blood in hydrophobia, acts as a poison, we do not know; but it certainly is a positive gain to have discovered the action of this poison on the ganglion cells. As Golgi remarks, it is not to be supposed that these changes in the ganglion cells are positively characteristic or peculiar to hydrophobia. Undoubtedly, a variety of poisons may produce the same set of changes in the ganglion cell. The point, however, is to investigate the great mass of obscure nervous diseases, and

ascertain by these cytological methods the evidence of the action of the poison, whether it be acute, intermittent, or slow and protracted in its exhibition. It can be seen therefore, that we stand on the threshold of a new conception of investigating nervous diseases, namely, by applying methods which give us exact information about the damage which occurs to ganglion cells in diseases, and the action of poisons on constituent elements of the nervous system. Formerly we could obtain no such data as these.

It is rather singular that the very striking and complex arrangement of the minute structures should have escaped attention until such a recent date. The explanation, however, is that the unravelling of the nerve fibre pathways, together with their origins and connections with ganglion cells, entirely engrossed the attention of investigators for the past fifty years. The use of bichromate fluids in the hardening of the nervous system, upon which the methods for the solution of these problems depended, renders the ganglion cell entirely unfit for cytological study, and for this reason until Nissl, by using such a fixative as alcohol in 1885, the wonderful details of cellular structure remained unknown. Up to this time and also until quite recently, observers who devoted their attention to neuro-pathology also used these same fluids, and were completely ignorant of a host of minute changes which may take place in the ganglion cell under the influence of disease, and yet apparently leave the cell in a normal condition when viewed by Müller's fluid hardening, which entirely shuts out of view cytological alterations. Thus, we can readily understand how comparatively little progress has been made in the study of neuro-pathology, and especially mental pathology, except in regard to changes in the nerve fibres, when the ganglion cell microcosm was entirely ignored.

In brief, until very recently only the outward morphology of the ganglion cell, both in the normal and abnormal nervous system was studied, and the work of the next two or three decades will be the most brilliant in clearing up the

great number of misconceived problems of neuro-pathology, when conducted along the lines of studying the cell, not from its outward form, but by its internal organization.

Two reasons, apparently, have retarded this most fruitful application of cell methods and cell knowledge to the problems of both neural and general pathology. In the first place, the extremely specialized training, and the unfortunately complicated terminology of the cellular biologist, requires a distinct course of study on the part of the pathologist. In the second place, the cells of the human body are not as favorable objects for cytologic study as those of the lower forms of animals. One has, therefore, to attain a broad and comprehensive insight into the elaborate internal arrangement of the cells of the human body, especially the ganglion cell, and to guard against hasty or erroneous interpretations of the cytological elements, whether under normal or abnormal conditions, to devote much time to the study of general cellular biology. An investigator who desires to apply the broadening conceptions of cytology to the problems of the human body, either under normal or abnormal conditions, and to plan out work in pathology from a cytological standpoint, should visit the marine or university biological laboratories, preferably the former, and become practically familiar with all of the complicated methods of the cytologist. He should study fertilization and cleavage of the ovum in the most favorable examples among the invertebrates and lower vertebrates. The cytologist for years has spent the greatest amount of time in this field, and in it has achieved his most brilliant results. Such an investigator should also study some of the lower forms of life which have very large cells, such, for instance, as *necturus salamandra* or *amphiuma*. The cells in such forms as these have thrown a great deal of light on general cytology, and show many features or detailed cell organization much more plainly than man and the higher vertebrates.

When familiar in this way with the introductory principles of the science of the cell, he may then to advantage

begin researches in the pathological cytology of many human diseases, which are so much in need of these investigations. Thus, the work of the succeeding years, in writing out the normal and pathological cytology of the human body, cannot be done by investigators who expect to plunge at once into the complicated cellular details of any particular set of cells of the body, as the various classes of ganglion cells, for instance, without much preparatory and comprehensive work, in general cellular biology. This warning is the more forcible in studying very delicate changes in cells under abnormal or diseased conditions, for the field is almost developed in the light of the most modern ideas, and may contain many pitfalls of error for the cell anatomist who has not studied the cell in the lower form of life and with absolute perfection of technique.

Even the chemistry of the various minutiæ of the nuclear and cytoplasmic organization is approaching a surprisingly accurate basis. This cytological chemistry must also be thoroughly mastered as well as the detailed structures of the internal cell structure. Malfatti and Lillienthal have shown that a series of chemical reactions, definite and concise in their graduations exist between certain basic and acid aniline dyes, and the materials composing the nuclear and cytoplasmic network. These exquisitely delicate reactions, indicating differences in the constitution, as well as in the location of certain granules or portions of the nuclear or protoplasmic reticulum must not be ignored in studying the problems of general or neural cell physiology and pathology. Finally, to consider the application of cytology to the cell which interests us most, namely, the ganglion cell, both under normal and abnormal conditions, it will be seen that these topics require investigation, with much training in general cellular biology, and should be investigated by observers who combine a thorough knowledge of minute cell anatomy with training in both general pathology and neuro-pathology. The most valuable and perfectly ideal kind of work in analyzing the complicated internal arrangement of ganglion cell structure should

come from men like Fleming, Boveri, the Hertwigs, Fol, Guignard, Van Beneden, Pfnitzner, Bütchli, Verworn and their colleagues, and Wilson and Watase in this country.

If such masters in cell anatomy combine also the training of the pathologist, and could join the two branches of research, especially in the ganglion cell, we should gain an enormous amount of knowledge that neither of the two branches of science single-handed could ever hope to attain, except in a superficial or even unreliable way.

It will be seen, therefore, that one of the most essential factors in the Pathological Institute will be to conduct these two branches of research hand in hand, and it will, therefore, be especially necessary to have one of the associates of the Institute a profound student of cytology, in order that he may direct work in the pathology and normal anatomy of the nervous system from this standpoint.

After having emphasized the value of the methods which display the minute anatomy of the ganglion cells to gain evidence of the action of the subtle body poisons, we may resort to a more specific consideration of these poisons. One particular group of these poisons was spoken of specifically, namely, the poisons which are associated with the development of bacteria within the body, and the circulation within the body of such a bacterial toxine, with its resultant effects, is known as toxæmia.

Now, hand in hand with the accumulation of the knowledge which resulted in the establishment of a group of certain poisons associated with the development of bacteria, another class of poisons has been very definitely grouped together, which are due to the retention in the body of more than the normal amount of certain secretions, or on the other hand, of an over-production of certain secretions, and these are somewhat loosely grouped together under the familiar name of intoxicants. The studies which have led up to the more definite knowledge of some of these intoxications are certainly among the most interesting experiments of the present century. The experimental work of the last several years on the thyroid gland, shows that it exerts a most

powerful influence upon the general nutrition of the body. If the thyroid be removed in dogs, a very intense poisoning occurs, and death seems to be due to the action of the poison on the nervous system. Incidentally it may be remarked that the action of this form of intoxicant on the nervous system can only be thoroughly appreciated by Nissl's method. Not only does a deficiency beyond a certain degree of the thyroid give rise to an intoxication, as in myxœdema, but an over-production or disturbance of the thyroid gland secretion may also give rise to an intoxication manifested by that puzzling and hitherto unexplained complexity of symptoms known as exophthalmic goitre. The precise nature of the investigations clearing up these two forms of thyroid intoxication, and explaining the cause of the clinical manifestations resultant from their actions, is certainly a most brilliant achievement of the past decade of medicine, and has been worked out quite entirely in the physiological and pathological laboratories.

We are led from such results to seek a similar explanation in several other obscure nervous diseases and inquire if they may not also be due to abnormal conditions of others of the ductless glands. We might expect to find in many nervous manifestations which have hitherto entirely baffled us in the search for the clue of a poison, especially with Nissl's method, evidences in the ganglion cells of intoxications like myxœdema, thyropravia and exophthalmic goitre.

Undoubtedly epilepsy is the manifestation of a temporary intoxication, which, if examined searchingly, and with a careful selection of an appropriate case for cytological study, will show traces of a poison which acts on the cortex similarly to those found in experimental thyropravia.

Unfortunately, however, we cannot expect to find any changes in the details of the ganglion cell organization, so that a series of changes due to toxæmia could be distinguished from an intoxication. We should not, for instance, expect to find in the pathological cytology of the ganglion cell any set of changes which would indicate specifically the changes due to rabies, or the changes due to thyro-

pravia. In cases of each of these diseases, the changes might be quite identical, and this is the result which the speaker has found in an extended set of researches in each of these sets of poisonings produced experimentally. The nervous manifestations in Addison's disease may also be regarded as an intoxication produced by deficiency of the suprarenal capsules. In fact, all of these hæmatopöetic organs which some years ago were grouped together as the ductless glands, the *terra incognita* of both the physiologist and pathologist, have to-day, as well as the marrow, become very important organs for investigation to both the general pathologist and neuro-pathologist, for we know that the exquisitely delicate maintenance of the normal conditon of the blood depends upon these organs, and if through disease of any of these hæmatopöetic organs, the ingredients of the blood fall out of harmony, the blood itself becomes a poison and may affect the nervous system very profoundly. For instance, in Addison's disease and the various anæmias the nervous system often manifests symptoms of poisoning, which ought to be recognizable from cytological study. It is interesting to note that Lichtheim pointed out some years ago that even such extensive changes in the nervous system as sclerosis of the spinal cord had been found associated with several of the blood diseases.

It is rather difficult at present to classify these different poisons of intrinsic origin, for the simple reason that we have not as yet definite enough knowledge of them except the bacterial toxines and the intoxicants from deficient or disturbed thyroid gland secretion. Probably at the present time it cannot be stated precisely whether in thyropravia the poison is due to a failure to eliminate certain materials from the blood, or whether the blood is deprived of certain additions from the thyroid, although the former hypothesis seems the more probable. It is again difficult to know whether to classify the poisonous action of the blood in the several anæmias and leucocythemias under the head of intoxicants. The absorption or failure to eliminate noxious materials from the gastro-intestinal tract certainly comes

under the head of intoxicants. The disturbed condition of the nutrition attending insufficient food or in starvation, gives rise to a condition of the body fluids which is practically equivalent to the condition of poison. Now, it will be seen that it is exceedingly important to investigate the effects of all these forms of poisoning upon the nervous system, both for the study of pathology of insanity and ordinary nervous diseases. It is equally important to have a more precise classification of these intrinsic poisons. We might, perhaps, for our purposes of studying their effects upon the nervous system, divide these poisons in an entirely tentative classification in order to gain a working basis, as follows:

No. 1. Bacterio-toxines—These accompany or are associated with the development of bacteria within the body.

No. 2. Hæmato-toxines—Poisons due to abnormal condition of the blood as in the several anæmias and leucocythemias.

No. 3. Intoxicants, subdivided into (*a*) hæmatopöetic intoxicants, for instance, such intoxicants as evince the manifestations of myxœdema, thyropravia, Basedow's disease and Addison's disease, and (*b*) intestinal intoxicants, such, for example as cephalalgias and epilepsy (?); and (*c*) Renal intoxicants. These comprise the several materials which were not properly eliminated by the kidneys, acting as poisons: for example, cerebral symptoms of uræmia; (*d*) pancreatic intoxicants, which cause the accumulation in the system of the materials which produce diabetes and its cerebral manifestations. (?)

The condition associated with starvation, if it can be likened to a poison, also that of acromegaly or other nutritional diseases wherein lesion of the pituitary body has been suspected, as well as malaria, are difficult to classify in any of these divisions. These last three conditions perhaps had best be classified among the hæmato-toxines, unless we wish to speak of the poison of malaria as being a hematozoon toxine, a word, however, which is quite unjustifiable, for we do not know positively whether the

hematozoon malariæ induces the poisonous effect of malaria by damaging the red blood corpuscles, or whether this red blood cell destruction is associated with the production of a toxine. The word cachexia is at the best a loose one, and what is indicated by cachexia and the poison producing a cachetic condition might well be placed in any of these classifications. For instance, the cachetic condition accompanying extensive tumor growths might be classed possibly as an intoxicant, a hæmato-toxine. The cachexia of marasmus would again be a hæmatone-toxine. The cachexia dependent upon a chronic suppurative condition might possibly be classed as a bacterio-toxine or hæmato-toxine. It is certainly appropriate to speak in detail of these various forms of intrinsic poisons, and even to attempt their unsatisfactory classification; for it will remind you of the very many ways indeed which the nervous system may be subjected to those changes which might ultimately lead to the several forms of insanity. The period at which the nervous system has been poisoned acutely by these poisons may be a long time in advance of the appearance of mental symptoms—so far in advance that it may have been overlooked, and yet be the direct cause in preparing the ground for insanity in later years, while leaving a stigma on the ganglion cells so that they are weakened against succeeding inroads of poisons.

(To be continued.)